Biological therapy updates in IBD

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Agenda

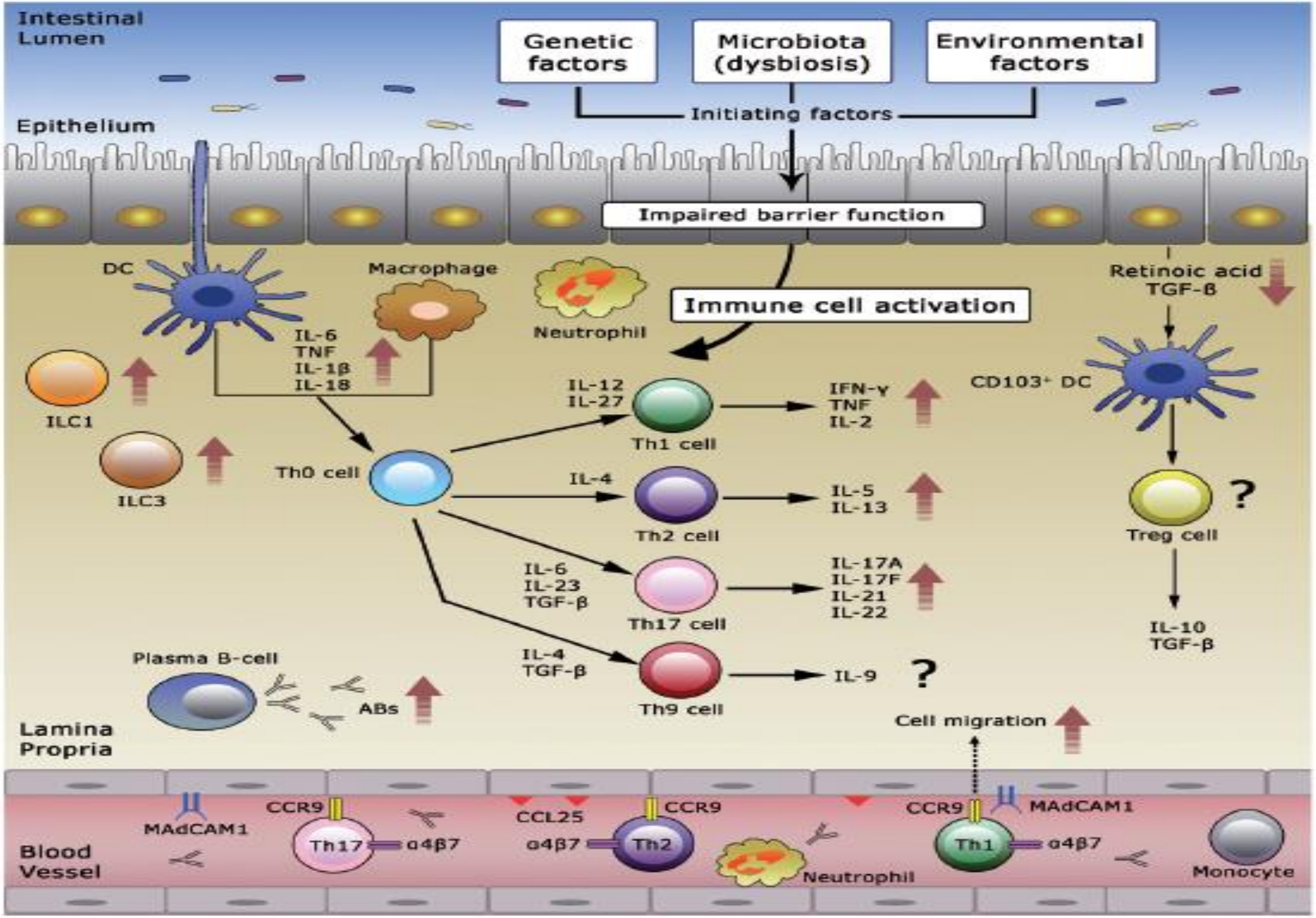
1-Mechanism of action
2-Preparation for starting
3-Biological agents
4-How to start?
5-Failure of response

Biological agents:

- **Inhibitors of proinflammatory cytokines**
  - ✓ **Anti – tumor necrosis factor – α (TNf – α blockers)**
    - **Infliximab** - **Adalimumab**
    - **Certolizumab(pegylated,CD)** - **Golimumab**

- **Adhesion molecule inhibitor (Natalizumab,Vedolizumab)**
- **Anti – inflammatory cytokkines**
  - **IL 10,IL 11** - **IL 12/23 p40 ab(ustekinumab)**
- **Inhibitors of proinflammatory cytokine receptor**
  - **Anti – IL 6 R**
- **Inhibitors of the polarization**
  - **Anti – IL – 2 receptor antibodies (Daclizumab, Basiliximab)**
  - **Anti IFN - ^{8} (Fontolizumab)**

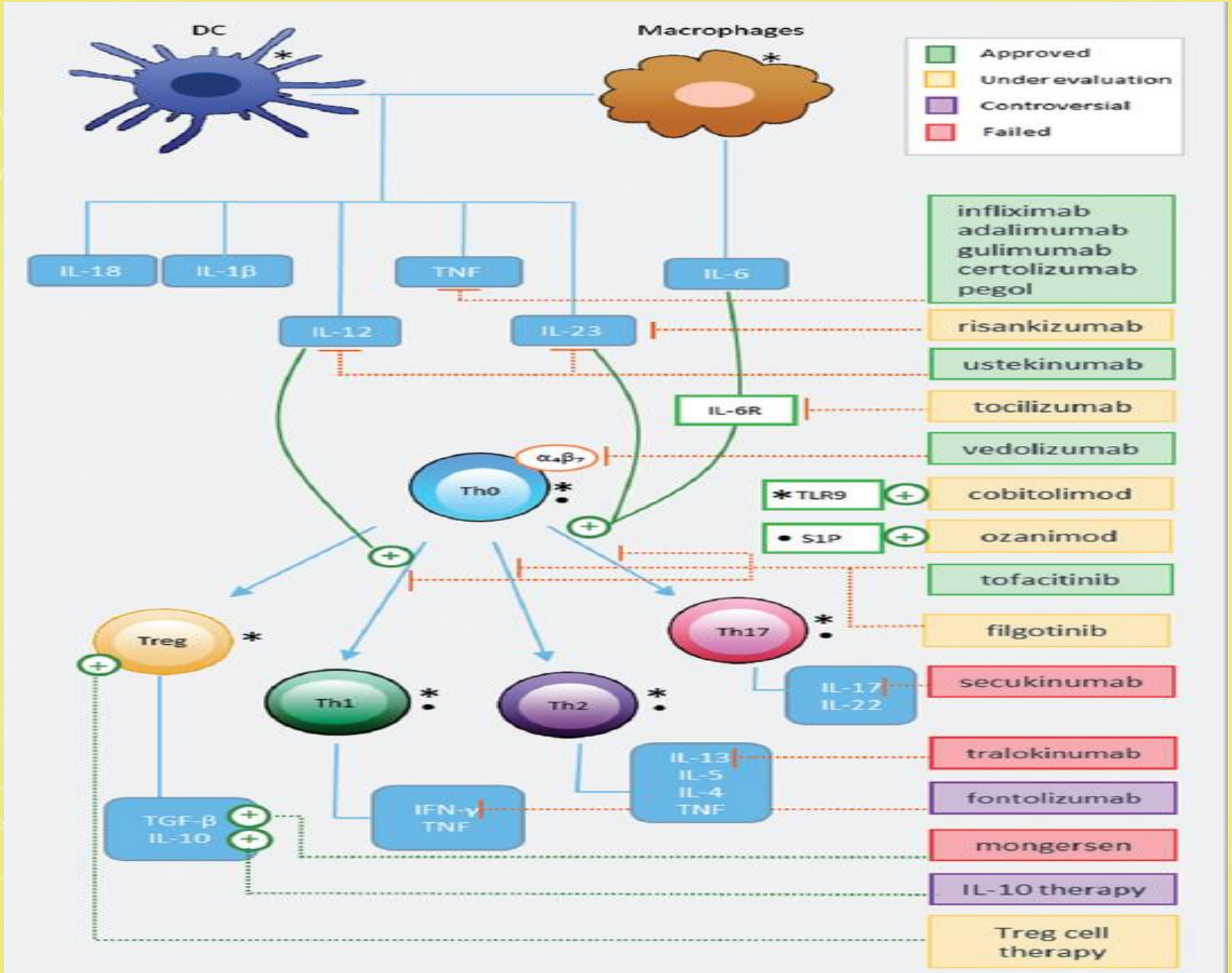
Introduction and mechanism of action



ANTI TNF

IL 12,23 AB

Adhesion molecules inhibitors

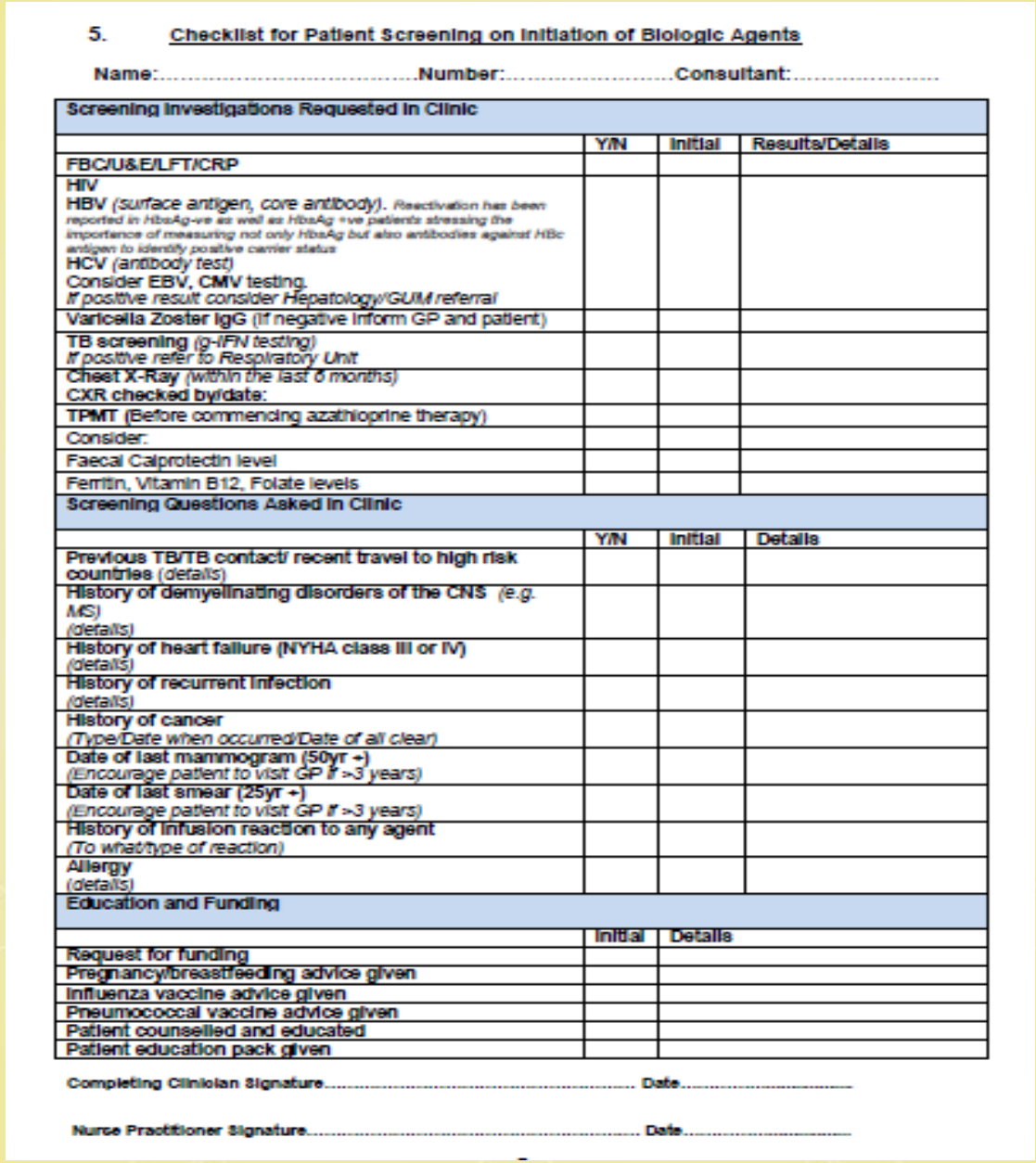

DC
Macrophages
Approved
Under evaluation
Controversial
Failed
IL-18
IL-1β
TNF
IL-6
IL-12
IL-23
IL-6R
α4β7
Th0
TLR9
S1P
Treg
Th17
Th1
Th2
IL-17
IL-22
IL-13
IL-5
IL-4
TNF
IFN-γ
TNF
TGF-β
IL-10
infliximab
adalimumab
gulimumab
certolizumab
pegol
risankizumab
ustekinumab
tocilizumab
vedolizumab
cobitolimod
ozanimod
tofacitinib
filgotinib
secukinumab
tralokinumab
fontolizumab
mongersen
IL-10 therapy
Treg cell
therapy

Preparing for biological therapy

Contraindications to Biological therapy

- Serious active infection
- Untreated latent tuberculosis
- Moderate-to-severe heart failure
- Known hypersensitivity to anti-TNF agents
- Multiple sclerosis or another neurological demyelinating disorder
- Optic neuritis
- Previous lymphoma or current malignancy
- Congenital or acquired immunodeficiency

Scott Levison ,et al., Biologics pathways for Inflammatory Bowel Disease in Adults ..NICE guidelines 2017



5. **Checklist for Patient Screening on Initiation of Biologic Agents**

Name:.....Number:.....Consultant:.....

Screening Investigations Requested in Clinic			
	Y/N	Initial	Results/Details
FBC/U&E/LFT/CRP			
HIV HBV *(surface antigen, core antibody). Reactivation has been reported in HbsAg-ve as well as HbsAg +ve patients stressing the importance of measuring not only HbsAg but also antibodies against HBc antigen to identify positive carrier status* HCV *(antibody test)* Consider EBV, CMV testing. *If positive result consider Hepatology/GUM referral*			
Varicella Zoster IgG (If negative inform GP and patient)			
TB screening *(g-IFN testing)* *If positive refer to Respiratory Unit*			
Chest X-Ray *(within the last 6 months)* CXR checked by/date:			
TPMT (Before commencing azathioprine therapy)			
Consider:			
Faecal Calprotectin level			
Ferritin, Vitamin B12, Folate levels			
Screening Questions Asked in Clinic			
	Y/N	Initial	Details
Previous TB/TB contact/ recent travel to high risk countries *(details)*			
History of demyelinating disorders of the CNS *(e.g. MS)* *(details)*			
History of heart failure (NYHA class III or IV) *(details)*			
History of recurrent infection *(details)*			
History of cancer *(Type/Date when occurred/Date of all clear)*			
Date of last mammogram (50yr +) *(Encourage patient to visit GP if >3 years)*			
Date of last smear (25yr +) *(Encourage patient to visit GP if >3 years)*			
History of infusion reaction to any agent *(To what/type of reaction)*			
Allergy *(details)*			
Education and Funding			
	Initial	Details	
Request for funding			
Pregnancy/breastfeeding advice given			
Influenza vaccine advice given			
Pneumococcal vaccine advice given			
Patient counselled and educated			
Patient education pack given			

Completing Clinician Signature..... Date.....

Nurse Practitioner Signature..... Date.....

Scott Levison ,et al., Biologics pathways for Inflammatory Bowel Disease in Adults ..NICE guidelines 2017

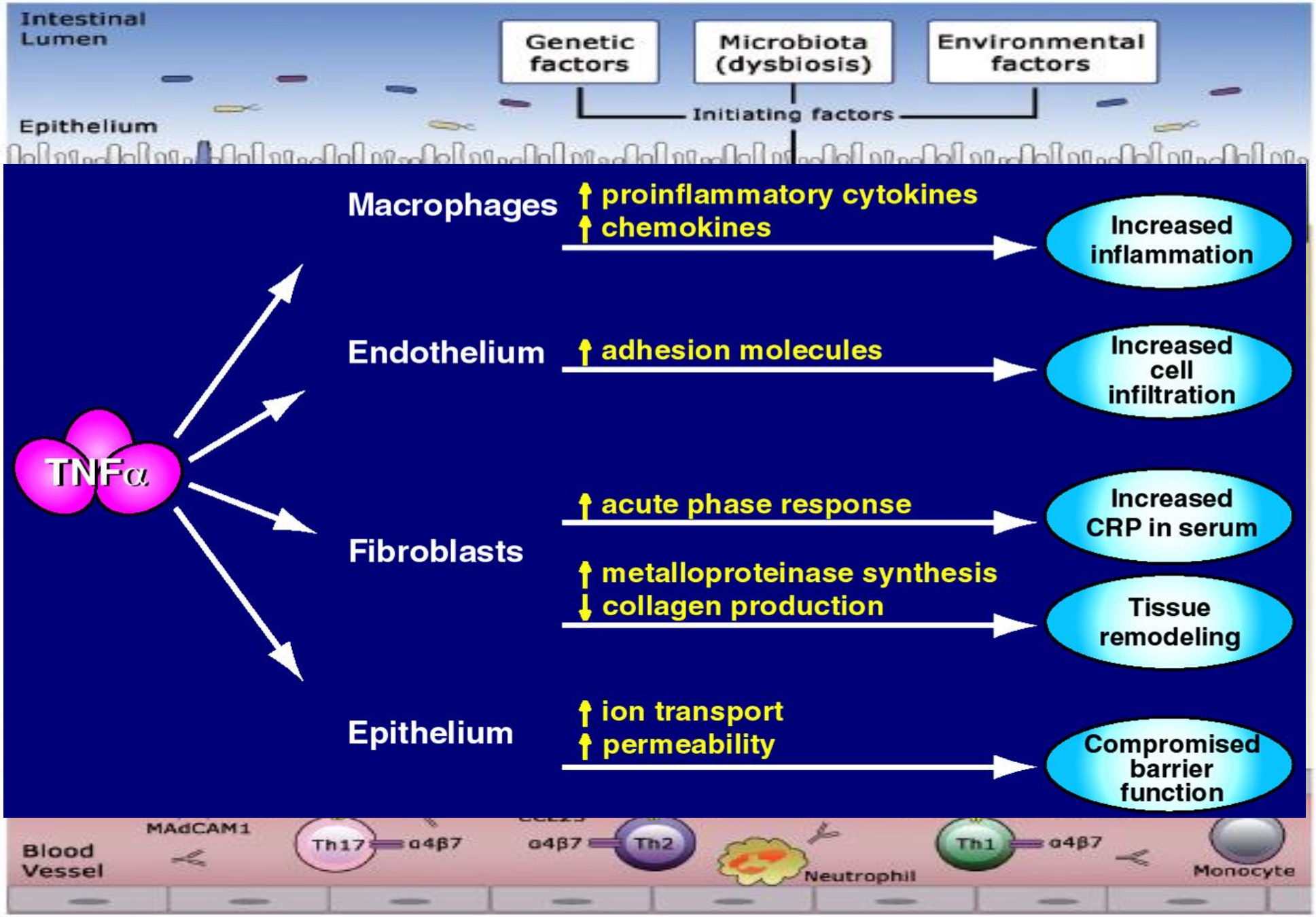
Screening Investigations Requested in Clinic			
	Y/N	**Initial**	**Results/Details**
FBC/U&E/LFT/CRP			
HIV **HBV** *(surface antigen, core antibody)*. *Reactivation has been reported in HbsAg-ve as well as HbsAg +ve patients stressing the importance of measuring not only HbsAg but also antibodies against HBc antigen to identify positive carrier status* **HCV** *(antibody test)* Consider **EBV, CMV** testing. *If positive result consider Hepatology/GUM referral*			
Varicella Zoster IgG (If negative inform GP and patient)			
TB screening *(g-IFN testing)* *If positive refer to Respiratory Unit*			
Chest X-Ray *(within the last 6 months)* **CXR checked by/date:**			
TPMT (Before commencing azathioprine therapy)			
Consider:			
Faecal Calprotectin level			
Ferritin, Vitamin B12, Folate levels			

Screening Questions Asked in Clinic			
	Y/N	**Initial**	**Details**
Previous TB/TB contact/ recent travel to high risk countries *(details)*			
History of demyelinating disorders of the CNS *(e.g. MS)* *(details)*			
History of heart failure (NYHA class III or IV) *(details)*			
History of recurrent infection *(details)*			
History of cancer *(Type/Date when occurred/Date of all clear)*			
Date of last mammogram (50yr +) *(Encourage patient to visit GP if >3 years)*			
Date of last smear (25yr +) *(Encourage patient to visit GP if >3 years)*			
History of infusion reaction to any agent *(To what/type of reaction)*			
Allergy			

Education and Funding		
	Initial	Details
Request for funding		
Pregnancy/breastfeeding advice given		
Influenza vaccine advice given		
Pneumococcal vaccine advice given		
Patient counselled and educated		
Patient education pack given		

Biological agents in IBD

- ✓Anti – tumor necrosis factor – α (TNf – α blockers):
  - Infliximab
  - Adalimumab
  - Certolizumab(pegylated,CD)
  - Golimumab


Intestinal Lumen
Genetic factors
Microbiota (dysbiosis)
Environmental factors
Initiating factors
Epithelium
Macrophages
proinflammatory cytokines
chemokines
Increased inflammation
Endothelium
adhesion molecules
Increased cell infiltration
TNFα
acute phase response
Increased CRP in serum
Fibroblasts
metalloproteinase synthesis
collagen production
Tissue remodeling
Epithelium
ion transport
permeability
Compromised barrier function
Blood Vessel
MAdCAM1
Th17
α4β7
α4β7
Th2
Neutrophil
Th1
α4β7
Monocyte

Anti-TNF → Infleximab(Remicade)

- **Chimeric monoclonal antibody (hybrid, 75% human & 25% mouse protein)**

- **Serum half life:** 9.5 days but still detectable in serum 8 weeks after infusion
- **Dose:** 5-10 mg/kg/dose IV infusion 0,2,6 w then every 8w.
- **Side effects:**
  - Infusion reactions (17%): fever, headache, chills, hypotension, abdominal pain
  - Infections (TB) (CXR, tuberculin test before Rx)
  - ↑ risk of malignancy (lymphoma)
  - Demylentation disorders
  - Auto-antibody formation (drug induced lupus)
  - Antibodies to infliximab (28%) (prevented by comb with immunmod -AZA

Sandborn W, et al, Gastroenterology 2005; 128:A-112-A-.

Anti-TNF → Adalimumab(Humera)

- **Character:** recombinant human immunoglobulin (1 gG1) monoclonal antibody containing only human peptide sequences (fully humanized)
- **Indication:**
  - ✓ Approved by FDA for treatment of RA
  - ✓ Currently, was assessed as an induction or maintenance or an alternative treatment in patients with loss of response and/or intolerance to infliximab
- **Dose** (mg, sc)
  - Induction: week 0 (40, 80 or 160), week 2 (20, 40 or 80)
  - Maintenance: 40
- **Adverse events:** (well tolerated compared to placebo)
  - Injection site reaction (30%)
  - Infrequent serious adverse events (infections, lymphoma)
  - Anti – adalimumab antibodies (0.7 %)
  - Cardiac events: worsening or de – novo CHF

Sandborn W, et al, Gastroenterology 2005; 128:A-112-A-

Anti-TNF → Golimumab(Simponi)

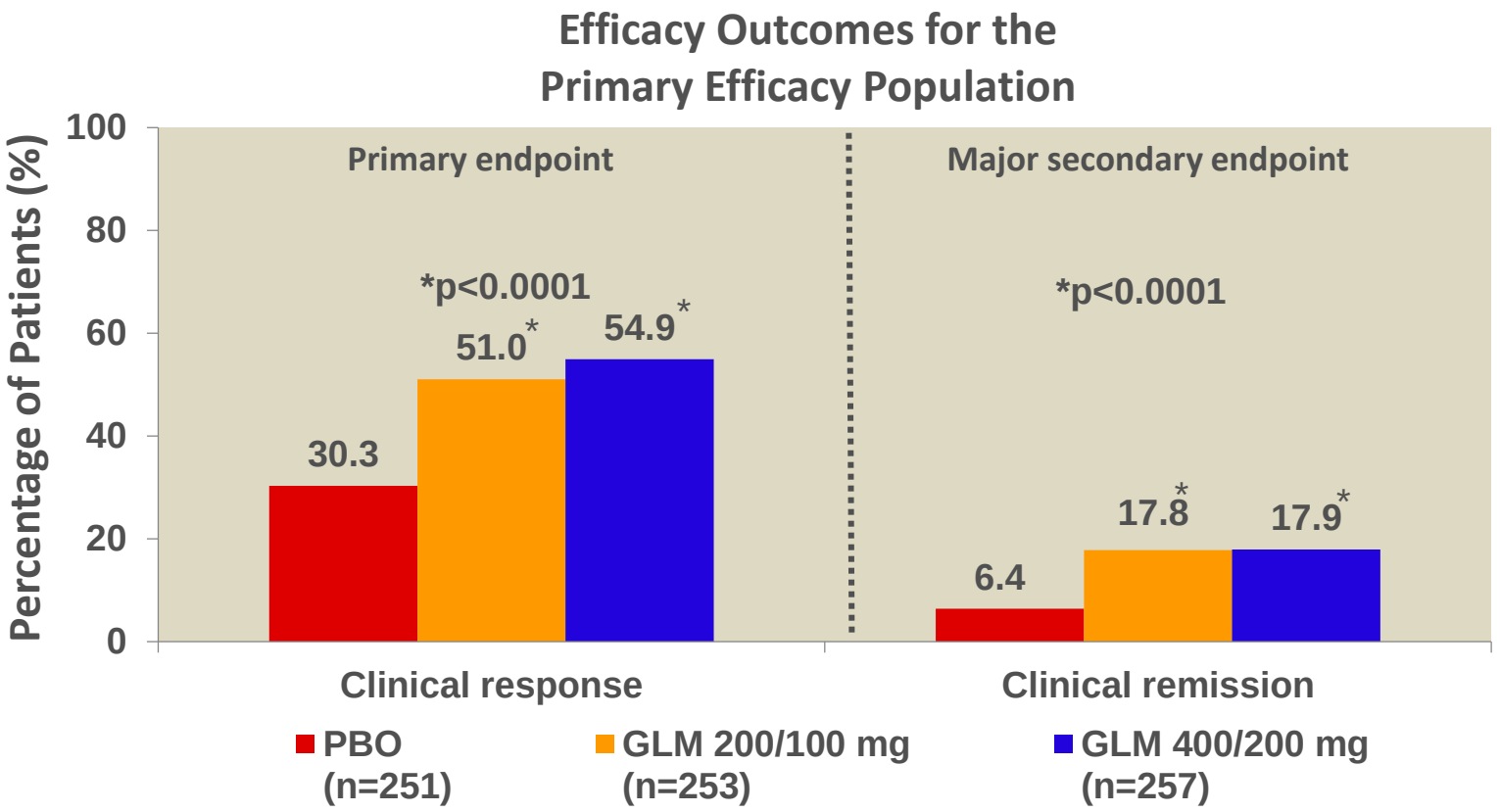
- One of the promising anti TNF agents in **moderate to severe active U.C**

- **Dose:** begins with 3 starter injections under the skin (subcutaneous injection): Two 100-mg injections on first day of treatment, followed by one 100-mg injection 2 weeks later. Maintenance: 100-mg injection every 4 weeks.

- **Efficacy: Study to Evaluate the Safety and Efficacy of Subcutaneous Golimumab Induction Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: PURSUIT SC**

Adapted from Sandborn et al. Gastroenterology 2014;146:85-95.

Efficacy Outcomes at Week 6



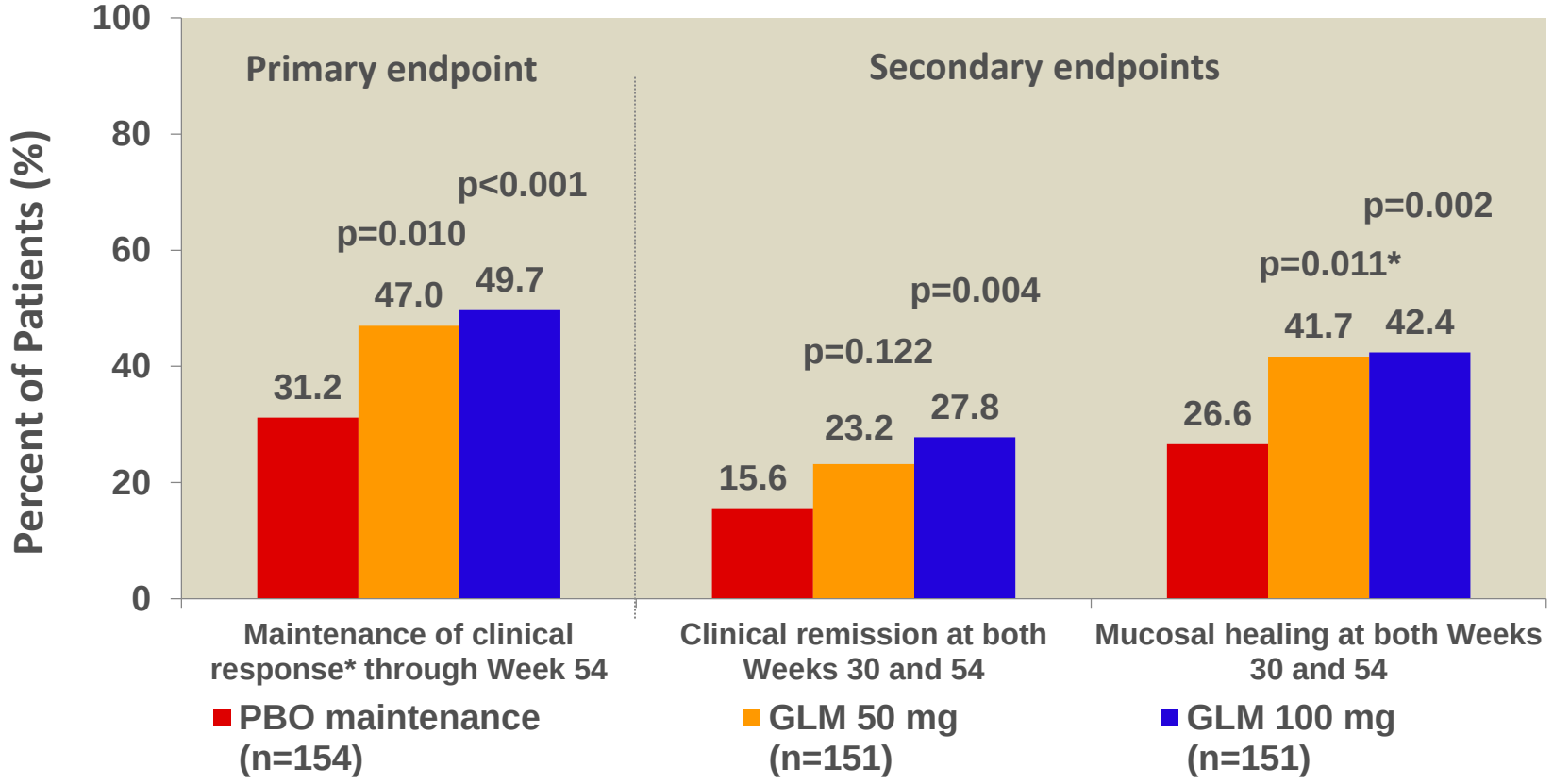
Clinical response: A decrease from baseline in the total Mayo score of ≥30% and ≥3 points, accompanied by either a rectal bleeding subscore of 0 or 1 point or a decrease from baseline in the rectal bleeding subscore of ≥1 point.

Clinical remission: A total Mayo score of ≤2 points, with no individual subscore of >1 point.

PBO: Placebo; GLM: Simponi

Adapted from Sandborn et al. Gastroenterology 2014;146:85-95.

Efficacy Outcomes Through Week 54 in Randomized Patients Following GLM Induction



Clinical response: A decrease from baseline in the total Mayo score of ≥30% and ≥3 points, accompanied by either a rectal bleeding subscore of 0 or 1 point or a decrease from baseline in the rectal bleeding subscore of ≥1 point

Sustained clinical remission: A total Mayo score of ≤2 points, with no individual subscore of >1 point at both Weeks 30 and 54

Mucosal healing: A Mayo endoscopy subscore of 0 or 1 point

*Nominal p-value since GLM 50 mg missed the previous secondary endpoint

PBO: Placebo; GLM: Simponi

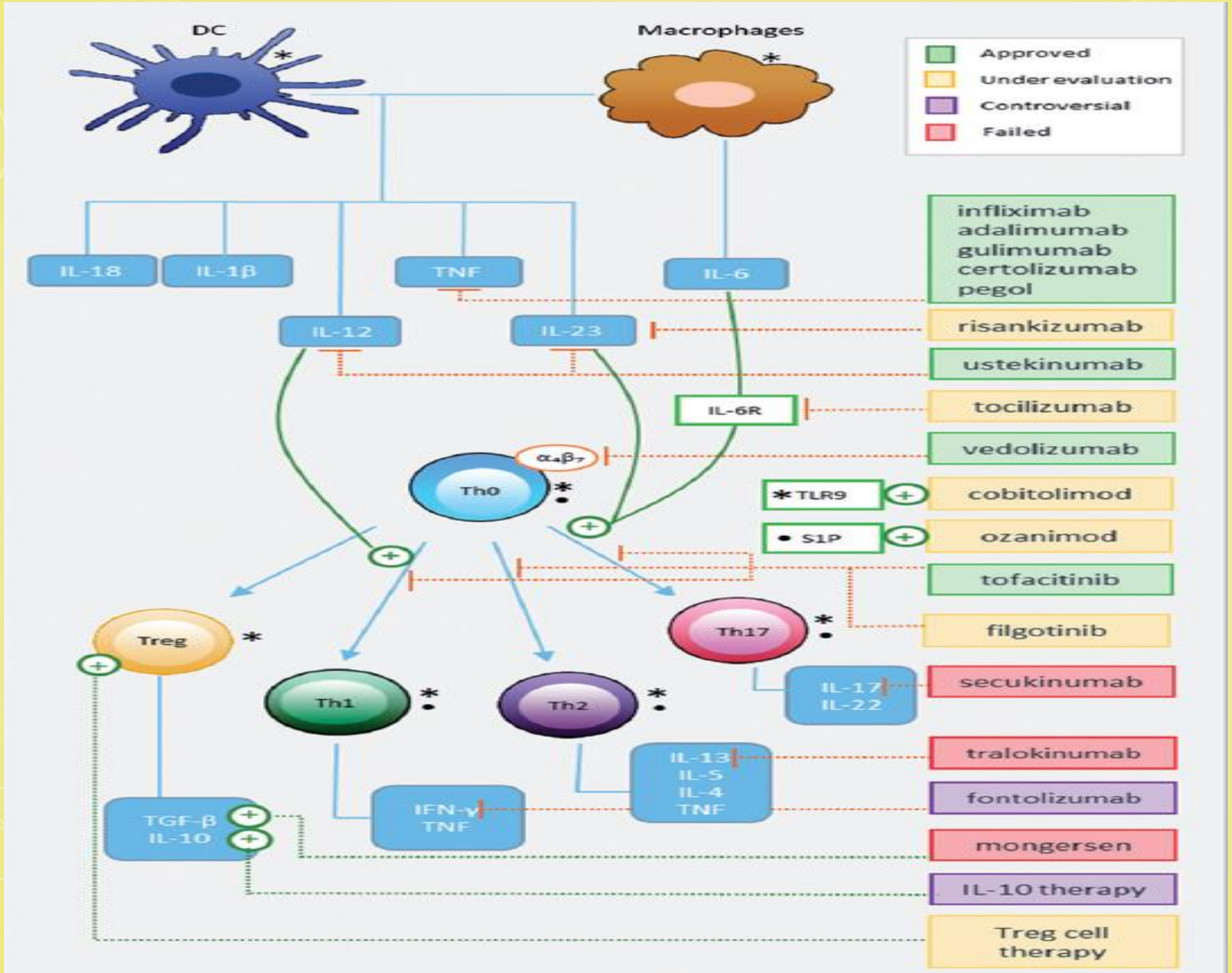
Adapted from Sandborn et al. Gastroenterology 2014;146:96-109.

Anti-TNF → Certolizumab(cimzia)

- **Moderate to severe crohns disease**

- **CIMZIA** is a PEGylated TNF (tumor necrosis factor) blocker and the first and only PEGylated biologic treatment for moderate **to severe rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and moderate to severe Crohn's disease.** The PEGylation process has been shown to help the medicine stay in the body.

- **Dose**:Initial dose: 400 mg subcutaneously (given as two subcutaneous injections of 200 mg) at weeks 0, 2, and 4
  Maintenance dose: 400 mg subcutaneously every 4 weeks in patients who obtain a clinical response
- **Efficacy: In the Precise -1** trial **662 patients** with moderately to severely active CD were randomized to receive certolizumab 400 mg or placebo at week 0, 2 and 4 then every 4 weeks until week 24. Clinical response at week 6 was 37% for certolizumab and 26% for placebo [$p < 0.05$].

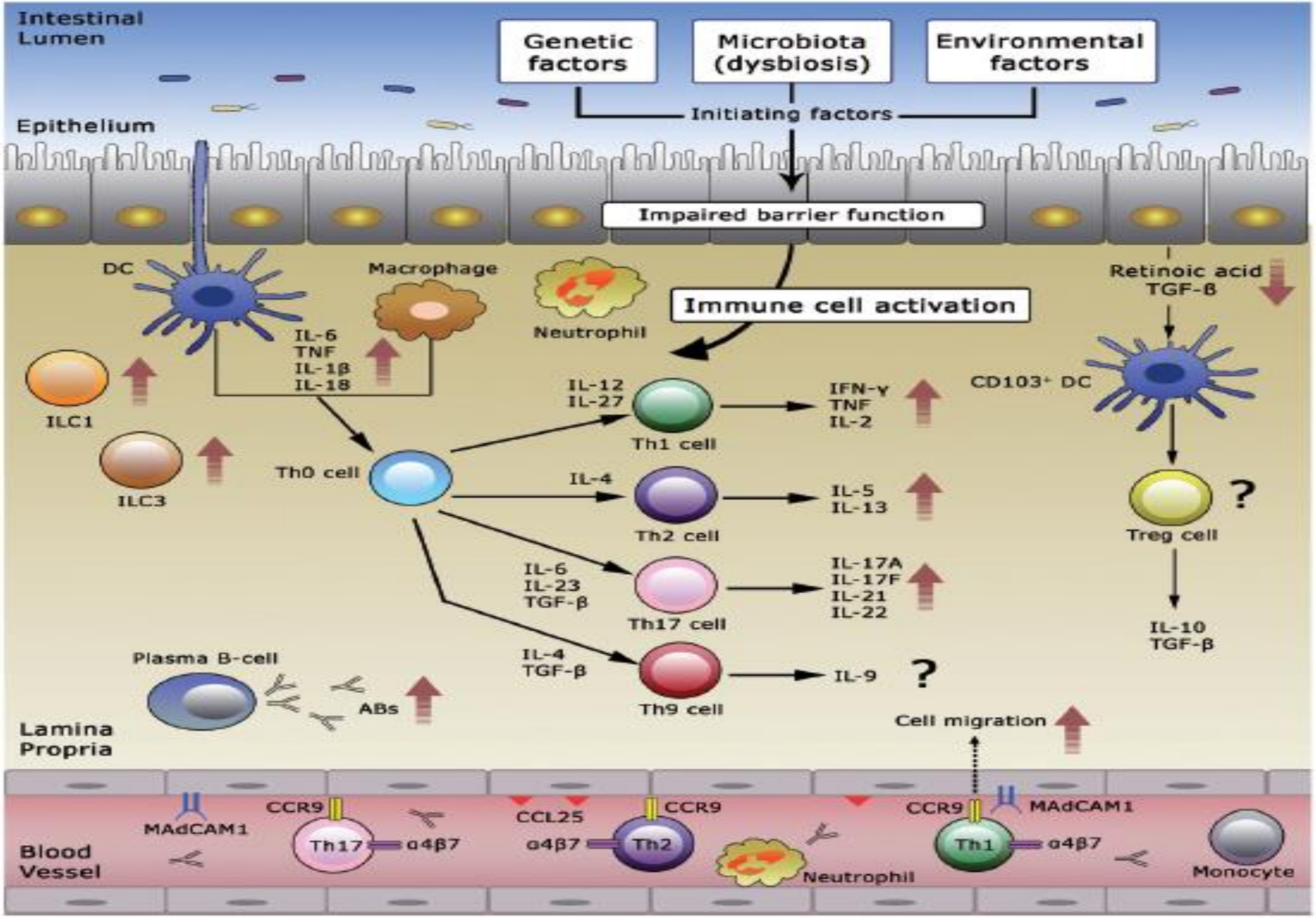

DC
Macrophages
Approved
Under evaluation
Controversial
Failed
IL-18
IL-1β
TNF
IL-6
IL-12
IL-23
IL-6R
α4β7
Th0
TLR9
S1P
Treg
Th17
Th1
Th2
IL-17
IL-22
IL-13
IL-5
IL-4
TNF
IFN-γ
TNF
TGF-β
IL-10
infliximab
adalimumab
gulimumab
certolizumab
pegol
risankizumab
ustekinumab
tocilizumab
vedolizumab
cobitolimod
ozanimod
tofacitinib
filgotinib
secukinumab
tralokinumab
fontolizumab
mongersen
IL-10 therapy
Treg cell
therapy

Ustekinumab(Stelara):anti-IL 12/23 p40 Ab

➢ Used in active psoriasis.

- *Ustekinumab* has also shown efficacy for inducing clinical response and clinical remission of **active CD.In** a placebo dose escalating controlled trial, 536 patients with active CD received 1, 3 or 6 mg/kg ustekinumab or placebo I. At 6 weeks, **40% of patients** treated with the highest dose of **6 mg/kg ustekinumab** achieved clinical response versus 24% of patients treated with placebo [*p* = 0.005], *but no improvement in remission rates was observed. Lower doses [1 and 3 mg/kg] were not effective.*

- **Side effects:** as other biological agents….allergy…increase incidence of T.B,lymphoma….infections… **reversible posterior leukoencephalopathy syndrome (RPLS) but rare..**



ANTI TNF

IL 12,23 AB

Adhesion molecules inhibitors

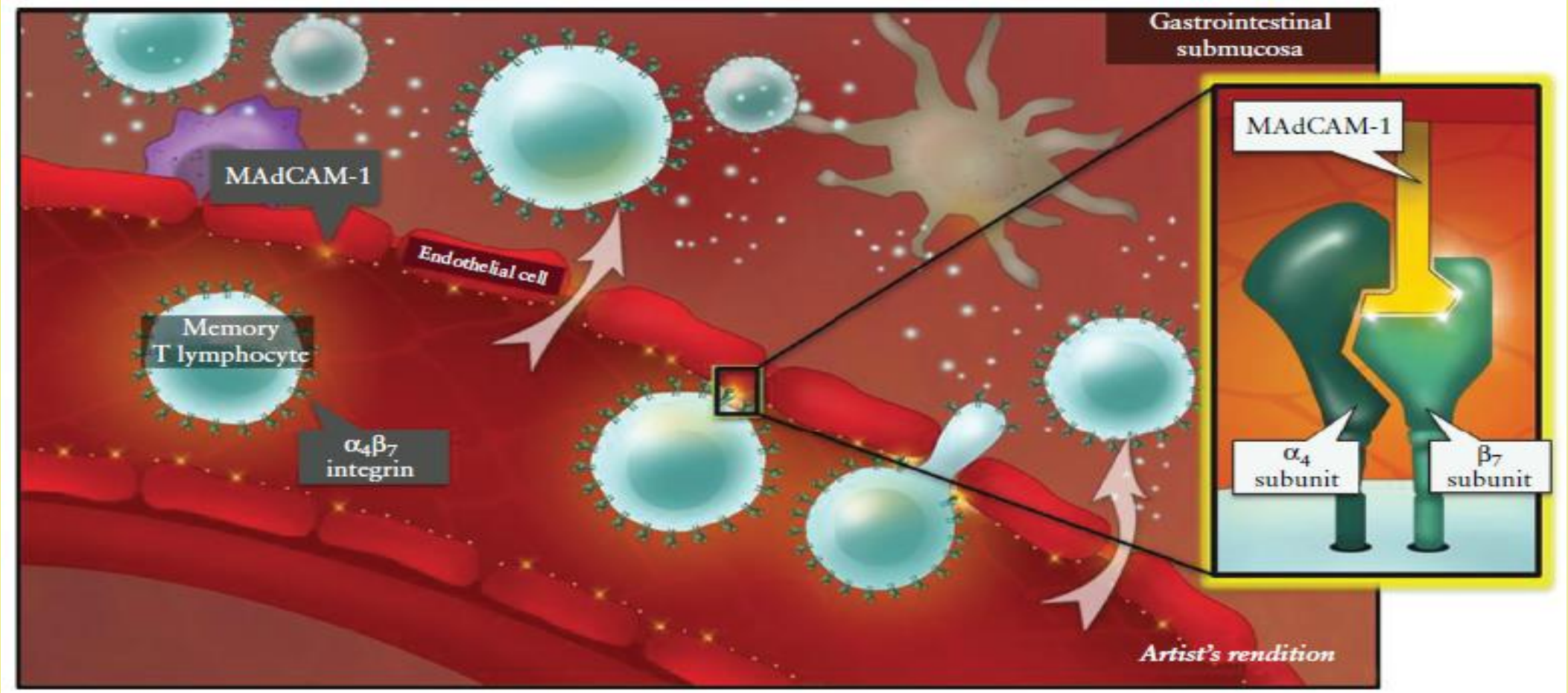
Adhesion Molecules inhibitors

- Prevents ***inflammatory white blood cells from migrating into tissue***.

- Can be used when patient has ***failed at least one anti-TNF medication.***

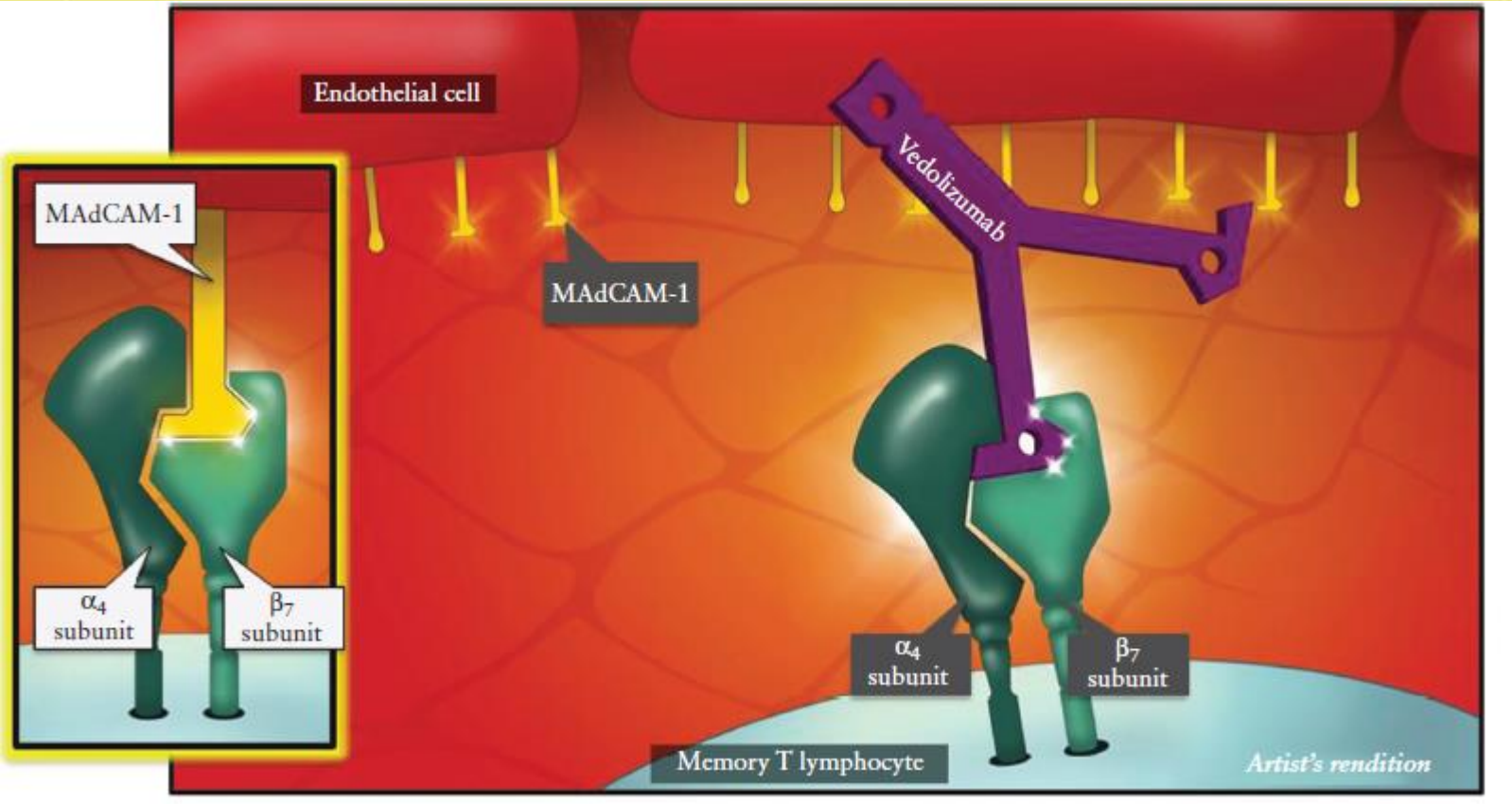
- ***Natalizumab***300mg/4weeks(I.V.)..***Vedolizumab***(300 mg IV at zero, two and six weeks and then every eight weeks).

Adhesion Molecules inhibitors
Vedolizumab(Entyvio)



Schematic representation of the interaction between ***α4β7 integrin and MAdCAM-1***. The α4β7 integrin is expressed on the surface of a discrete subset of memory T lymphocytes that preferentially migrate into the gastrointestinal tract. The α4β7 integrin binds to MAdCAM-1 on the surface of endothelial cells to initiate extravasation into gastrointestinal submucosa. Interaction of α4β7 integrin with MAdCAM-1 has been implicated as an important contributor to the chronic inflammation that is a hallmark of UC and CD.

An Overview of the Mechanism of Action of the Monoclonal Antibody Vedolizumab, Tim Wyant,a Eric Fedyk,b Brihad Abhyankar, *Journal of Crohn's and Colitis*, 2016, 1437–1444



Schematic representation of the interaction between α4ß7 integrin and vedolizumab. Vedolizumab, a humanised monoclonal antibody, binds to the α4ß7 integrin receptor expressed on the surface of a discrete subset of memory T lymphocytes and blocks the interaction of these cells with MAdCAM-1. Vedolizumab binds to the specific conformation of the α4ß7 heterodimer with an epitope for the ß7 subunit. Inset: the adhesion molecule MAdCAM-1 is shown interacting with α4ß7 integrin. MAdCAM-1, mucosal addressin cell adhesion molecule-1.

An Overview of the Mechanism of Action of the Monoclonal Antibody Vedolizumab, Tim Wyant,a Eric Fedyk,b Brihad Abhyankar, *Journal of Crohn's and Colitis*, 2016, 1437–1444

- **Side effects:** **as** other biologics….headache…allergy….infections….liver proplems….

- **Uses:** 1-Moderate to severe ulcerative colitis (UC) :AS 1st line or after failure of other biologics

2-Moderate to severe crohns disease:As 1st line or after failure of other biologics

- **Recommended dosage** in UC and CD: 300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks, then every eight weeks thereafter.

- Discontinue ENTYVIO in patients who do not show evidence of therapeutic benefit by Week 14

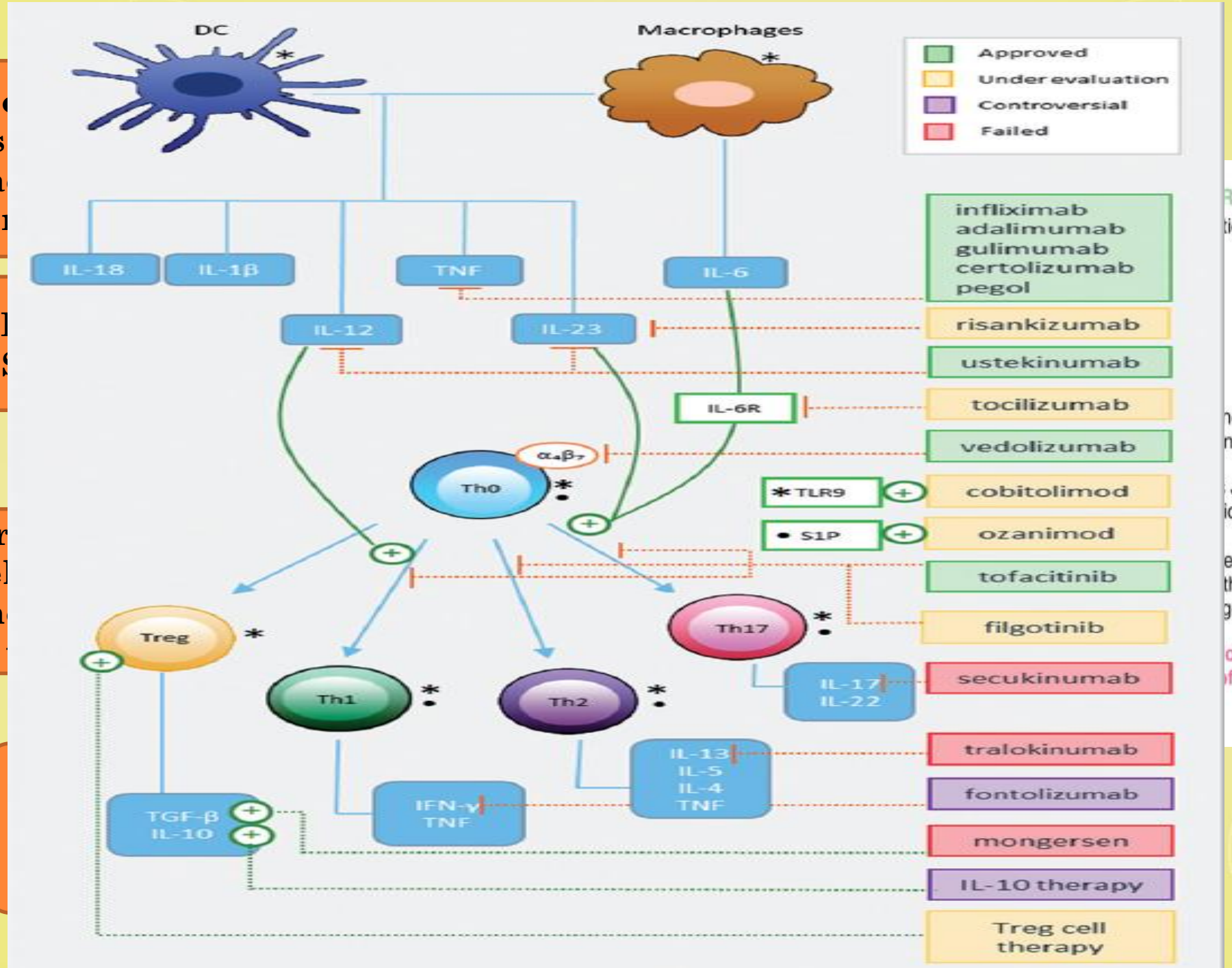
An Overview of the Mechanism of Action of the Monoclonal Antibody Vedolizumab, Tim Wyant,a Eric Fedyk,b Brihad Abhyankar, *Journal of Crohn's and Colitis*, 2016, 1437–1444

What is new???

ECCO guidelines 2017

Other novel compounds such as Janus kinase inhibitors, anti-IL-6 antibodies, anti-Madcam antibodies and SMAD7 antisense oligonucleotides are being actively tested. For instance, tofacitinib, an oral Janus kinase inhibitor, has been tested with promising results in UC,[342] but failed to demonstrate better response than placebo in a phase II trial in CD.[343] Mongersen, an oral SMAD7 antisense oligonucleotide, was clearly better than placebo in obtaining clinical response, with a clear dose–response curve, in a clinical trial[344] that was criticised by lack of objective definition of response and is awaiting confirmation in other studies.

Tofacitinib??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TGF-β
IL-10
infliximab
adalimumab
gulimumab
certolizumab
pegol
risankizumab
ustekinumab
tocilizumab
vedolizumab
cobitolimod
ozanimod
tofacitinib
filgotinib
secukinumab
tralokinumab
fontolizumab
mongersen
IL-10 therapy
Treg cell
therapy

Its efficacy for the treatment of moderately to severely active ulcerative colitis was demonstrated in ***three controlled clinical trials***

The OCTAVE Induction 1 and 2 trials were identical enrolling 598 and 541 patients with mo
me

Considering the benefits versus risks, tofacitinib could be an attractive option for *rescue therapy* for patients with UC in whom anti-tumor necrosis factor therapy fails

At
pa
pla **s**
biologic-naive patients.

The OCTAVE Sustain maintenance trial and received either 5 mg or 10 mg of tofacitinib twice daily or placebo. **After 52 weeks**, 34.3% (5 mg) and **40.6% (10 mg**) of tofacitinib-treated patients were in remission compared with 11.1% of patients receiving placebo (*P* < .001).

Tofacitinib: Emerging Therapy for Ulcerative Colitis, Arthur M. Barrie;Medscape gastroenterology;jan.2018

Xeljanz, made by Pfizer Labs, was previously approved in 2012 for rheumatoid arthritis and in 2017 for psoriatic arthritis

FDA approves new treatment for moderately to severely active ulcerative colitis

The U.S. Food and Drug Administration today expanded the approval of Xeljanz (tofacitinib) to include adults with moderately to severely active ulcerative colitis. Xeljanz is **the first oral medication** approved for chronic use in this indication.

www.FDA.gov/NewsEvents/Newsroom/.../ucm609225.htm,2018

- **Side effects:** diarrhea, elevated cholesterol levels, headache, herpes zoster (shingles), increased blood creatine phosphokinase, nasopharyngitis (common cold), rash and upper respiratory tract infection

- Use of Xeljanz in *combination with* biological therapies for ulcerative colitis or with potent immunosuppressants, such as azathioprine and cyclosporine, is not recommended???

- Tofacitinib may have another advantage over biologic therapies owing to its ***short half-life of 3 hours***, which is also beneficial during pregnancy.

- Clearance of tofacitinib is not affected by disease activity, so ***therapeutic drug monitoring will probably not be necessary.***

Examples of biologics for inflammatory bowel disease, approved and under development Gastroenterol Rep (Oxf)

Name	Primary target	FDA-approved indication
Infliximab (Remicade®)	TNF	CD, UC
Adalimumab (Humira®)	TNF	CD, UC
Certolizumab (Cimzia®)	TNF	CD
Golimumab (Simponi®)	TNF	UC
Natalizumab (Tysabri®)	alpha-4 integrin	CD
Vedolizumab (Entyvio®)	alpha-4-beta-7 integrin	CD, UC
Ustekinumab (Stelara®)	IL-12/23	N/A
Tofacitinib(xeljanz)	JAK inhbitor	UC
Etrolizumab	beta-7 integrin	N/A
Anrukinzumab	IL-13	N/A

a) Initiating treatment with a biologic

- The choice of biologic used should be guided by clinical judgement, national or local guidance, and the overall value proposition offered by the individual medicines. The rationale for choice should be documented.
- If more than one treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage, price per dose and treatment frequency).
- When the biologic treatment with a particular drug has been selected, the least expensive product, either biosimilar or originator should be prescribed.
- If the least expensive product is not prescribed, the reasons why must be documented and made available to commissioners if required.
- Where NICE has already recommended the originator biological medicine, the same guidance will apply to the biosimilar medicine.

Scott Levison ,et al., Biologics pathways for Inflammatory Bowel Disease in Adults ..NICE guidelines 2017

Pathway A

Crohn's Disease Biologic Pathway

If contraindication to anti TNF therapy
=
Use Ustekinumab or Vedolizumab 1st line

Moderately-to-Severe active Crohn's (TA 187)
Failure or intolerance of immunosuppression
Adalimumab SC
Infliximab IV
Ustekinumab IV then SC (**TA 456**)

Active Fistulating CD (TA 187)
Infliximab = 1st Line
Consider Adalimumab/ Ustekinumab / Vedo (if contraindication to infliximab)

Suitable for clinical trial ?

s response at 12-16 weeks = NICE REVIEW

Clinical respons
Bloods +/- Fa

Good Response

Partial r

Primary non-response
No clinical response to initial biologic therapy

Optimise anti TNF (drug trough levels = Pathway C)

Add/ optimize immunosuppres ble + not already on)

Alternative anti TNF (if neutralizing Ab's)
or, Ustekinumab (TA 456)
or, Vedolizumab (TA 352)

Surgery

If levels/ antibodies not corrected, repeat cycle.
Allow x2 repeats then for alternative therapy.

Assess response (after ~ 8/52)
e.g. repeat drug and antibody levels

Good Clinical response

Poor response

Continue scheduled prescribing + clinical review for response

Alternative anti TNF (if neutralizing Ab's)
or, Ustekinumab (TA 456)
or, Vedolizumab (TA 352)

Clinical trial

Surgery

Clinical response (HBI)
Faecal calprotectin
Colonoscopy /
Radiology (Small bowel)

Reassess response at 12/12
= NICE REVIEW

Remission*

Partial/Incomplete response

Lost response

Consider stopping biologic + Maintaining immunosuppressant

Continue + optimise biologic therapy +/- immunosuppressant.

Switch to alternative biologic Ustekinumab (TA 456)

* Remission for biologic cessation is defined as asymptomatic and biochemical and/or endoscopic and/or radiological evidence of healing.

Ulcerative Colitis Biologics Pathway

NICE CG 166

Moderately to severely active UC

Acute severe UC

Anti-TNF (TA 329)
Infliximab (IV), Golimumab (s/c), Adalimumab (s/c)

Vedolizumab (IV) (TA 342)

Infliximab (IV) (TA 163)
5mg/kg

Ciclosporin (IV)
2mg/ kg/ 24 hours IV

Assess response
by 12/52

Clinical response (UCDAI)
Bloods +/- Faecal calprotectin

Assess response
by 12/52

Clinical response (UCDAI)
Bloods +/- Faecal calprotectin

Assess response
daily **

**Consider an extra 5mg/kg IFX if no clinical benefit + extensive haemorrhagic colitis

Assess response
daily

Poor response

Clinical response

Clinical response

Poor response

Clinical response

Optimise anti-TNF (trough & ab levels)
(Pathway C)
Add/ optimize immunosuppression
Consider a Flexible Sigmoidoscopy

Wean steroids
Commence Azathioprine

Colectomy

No benefits switching between Ciclo and IFX if fail one therapy.
(Maser EA, 2008)

Commence oral Ciclosporin
(5mg/kg in two divided doses)

Commence Azathioprine

Co-trimoxazole 480mg/day prophylaxis (if on dual Rx)

Oral Ciclo = for 3-6/12

Assess response
after ~ 8/52

Clinical response

Assess response
at 3/12

Repeat cycle x 2 times
if needed to optimise

Continue scheduled prescribing + clinical review
(Drug and Ab monitoring if loss of response)

Remission for UC:
Total or partial Mayo score <2 (no score >1) + steroid free

Response in UC:
↓ Total Mayo ≤3; ↓ Partial Mayo ≤2

Poor response

Assess response
at 12/12

Colonoscopy / sigmoidoscopy
Calprotectin
Clinical response

Poor Response

Response

Alternative anti-TNF
(if neutralizing Ab's)
or
Vedolizumab
(TA 342)

Clinical trial

Surgery

Alternative Biologic Therapy

Stop Ciclosporin
+ continue Aza

Remission

Partial / Incom-plete response

Lost response = switch therapy

Response

Partial response = optimise therapy

No response = Colectomy

Consider stopping biologic and maintaining immunosuppressant

Optimise biologic + immunosuppressant

Alternative biologic/ Surgery

When to assess response?
How to assess?

12 weeks
Clinically,Laboratory,Endoscopically

Failure of response

Failure of response:

Roda,et al., Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management: Clinical and Translational Gastroenterology (2016) 7, e135; doi:10.1038.

Patient on TNF alpha antagonist with active disease

Verify if symptoms are due to active IBD (CRP, calprotectin, CMV ,endoscopy,imaging) and confirmed compliance

NO

Treat the cause(CMV,Clostridium difficile)

Yes

So, Verify drug compliance/perform therapeutic drug monitoring(Antibody level and Trough level of the drug)

No/low drug, high antibodies

Best option:
Switch to another anti-TNF
Alternative: add immunemodulator

Adequate drug, no antibodies

Best option:
Switch out of therapeutic class (Infleximab to vedolizumab)
Or switch within the class(Infleximab to adalimumab)

Subtherapeutic drug levels, No antibodies

Best option:
Dose escalation.e.g:increase dose of infleximab(7.5-10mg/kg)or increase the frequency(may be every 6 weeks).

Take home message

- Managemant of IBD is a multidisplinary approach .
- Management of IBD is rapidly evolving and role of biologics is crucial.
- There are many biological agents either approved by FDA or still under evaluation.

THANK
YOU

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